

## HÆMODYNAMIC STUDIES WITH METHYLDOPA: EFFECT ON CARDIAC OUTPUT AND RESPONSE TO PRESSOR AMINES

BY

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Methyldopa has been shown to be an effective hypotensive agent both in animals and in man (Oates *et al.*, 1960), and valuable in the treatment of hypertension, particularly in the management of mild or moderately severe cases (Dollery and Harington, 1962; Bayliss and Harvey-Smith, 1962). Pharmacological activity resides entirely in the L-isomer (Gillespie *et al.*, 1962). The mechanism of the anti-hypertensive action of methyldopa is not fully understood. Although known to be an inhibitor of decarboxylase (Sourkes, 1954), and thus potentially capable of reducing the biosynthesis of noradrenaline and other pressor amines, there is evidence that the cardiovascular effects of the drug are independent of this mechanism, and more closely related to depletion of noradrenaline from sympathetic nerve endings (Hess *et al.*, 1961). The present paper reports certain further observations on the clinical pharmacology of methyldopa, in particular measurements of the cardiac output before and after treatment, and the effect of the drug on the response to pressor amines.

### SUBJECTS AND METHODS

Because the action of methyldopa is slow in onset, even after intravenous injection, it has been found impracticable to record the acute effects of the drug in a single study. Paired studies have therefore been carried out on 10 hypertensive patients, first before commencement of oral treatment and again after a period of 4 to 10 days' treatment in doses of 0.75–2.0 g. daily. The patients ranged in age from 33 to 62 years, had not previously been receiving hypotensive treatment, and were considered to be suitable subjects for long-term treatment with methyldopa. All had high levels of resting blood pressure (Table I), but none showed exudative retinopathy or papilloedema. None of the patients had severe renal failure, the highest urea level being 46 mg./100 ml.

Blood pressure was recorded from an indwelling catheter in the femoral artery, and intravenous injections were given through a polythene catheter, the tip of which lay in the superior vena cava. Cardiac output was measured by indicator dilution using the dye Coomassie blue and recording with an arterial cuvette and Cambridge dye recorder. Arterial blood was drawn through the cuvette by a constant speed syringe pump at a rate of 35 ml./min. The curves were recorded from the cuvette in the normal way and the whole curve to the point of recirculation was sampled by the motor-driven syringe. The concentration in this mixed blood sample was used to calibrate the integrated curve area over the time of sampling. <sup>131</sup>I-labelled human serum albumin was added to the Coomassie blue dye before injection so that each injection contained about 2  $\mu$ c. Instead of estimating the dye concentrations, the radioactivity in the blood samples was

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TABLE I  
RESTING SUPINE BLOOD PRESSURE AND CARDIAC OUTPUT BEFORE AND AFTER TREATMENT WITH METHYLDOPA

Case No.	Blood pressure (mm. Hg)		Cardiac output (l./min.)	
	Before	After	Before	After
1	202/110	137/74	5.3	3.9
2	232/97	176/76	4.7	4.0
3	256/97	202/74	4.9	4.0
4	241/117	197/96	4.7	4.4
5	211/107	172/85	5.5	4.9
6	211/100	177/91	7.1	7.7
7	200/111	181/96	5.2	6.1
8	210/95	195/89	6.1	5.6
9	206/108	209/109	4.6	5.0
10	187/96	195/99	4.4	5.1
Mean	216/104	184/89	5.3	5.1

counted. The method of calibrating the dye curves with an integrated sample is essentially the same as that devised by Emanuel, Lacy, and Newman (1957). Calibrated curves were usually drawn at the beginning, middle, and end of each study while other curves were drawn using dye without  $^{131}\text{I}$  and using the average calibration factor. The linearity of the recording apparatus had been tested previously on a series of concentrations of Coomassie blue in water and in oxygenated blood and found to be satisfactory over the range of concentrations actually recorded during studies on patients.

Three to five observations of resting supine blood pressure and cardiac output were made for all patients both before and after treatment with methyldopa. In five patients complete data were also obtained on tilting to  $50^{\circ}$ – $60^{\circ}$  in the feet down position.

The response of the arterial pressure to performance of the Valsalva manoeuvre and to graded doses of noradrenaline was studied in all patients, both before receiving methyldopa and while on treatment with the drug. Noradrenaline was administered in single doses of  $1\text{--}8\text{ }\mu\text{g.}$ , made up to a standard volume of 2 ml. and given by rapid intravenous injection. The effect of tyramine in intravenous doses of  $1.25\text{--}5\text{ mg.}$  was also observed in six patients.

## RESULTS

*Resting Cardiac Output.* The average values for resting supine blood pressure and cardiac output before and after methyldopa treatment are shown in Table I. The clinical response to methyldopa in the period between studies had been satisfactory for all patients, as judged by reduction of blood pressure in the ward and the sedative influence: however, an adequate fall in supine blood pressure (more than 30 mm. systolic) at the second study was obtained in only 6 of the 10 patients. The heart rate was slowed by methyldopa in most cases, falling from a mean of 76 to 70 beats a minute.

Considering the group as a whole there was a small fall in supine blood pressure after treatment with methyldopa (from 216/104 to 184/89 mm. Hg) but this was not accompanied by a significant overall change in cardiac output. However, those patients in whom the greatest reduction in blood pressure was obtained (Cases 1–6 in Table I) tended to show a fall in cardiac output, which was not seen in those where the blood pressure was lowered to a lesser degree. The fall in blood pressure was proportionately greater than the cardiac output, and the calculated peripheral resistance was lower after treatment in all except one case.

*Effect of Tilting.* Before treatment with methyldopa tilting into the feet down position produced a fall in both blood pressure and cardiac output in 4 of the 5 patients tested, the remaining patient showing a rise (Table II). The average blood pressure fall was from a resting supine value of 221/103 to 190/99 mm. Hg on tilting, while the average cardiac output fell from 5.6 to 4.7 litres a

TABLE II  
EFFECT OF TILTING ON BLOOD PRESSURE AND CARDIAC OUTPUT BEFORE AND AFTER TREATMENT WITH METHYLDOPA

Case No.	Blood pressure (mm. Hg)		Cardiac output (l./min.)	
	Supine	Tilted	Supine	Tilted
2 { Before .. ..	232/97	212/100	4.7	3.5
2 { After .. ..	176/76	151/68	4.0	2.5
4 { Before .. ..	241/117	181/101	4.7	2.9
4 { After .. ..	197/96	163/83	4.4	3.8
5 { Before .. ..	211/107	192/104	5.5	4.0
5 { After .. ..	172/85	150/85	4.9	4.3
6 { Before .. ..	211/100	147/70	7.1	6.0
6 { After .. ..	177/91	153/87	7.7	5.8
8 { Before .. ..	210/95	218/122	6.1	7.4
8 { After .. ..	195/89	125/75	5.6	3.7

TABLE III  
EFFECT OF NORADRENALINE BEFORE AND AFTER TREATMENT WITH METHYLDOPA (MEAN FIGURES)

		Rise in blood pressure (mm. Hg)	Duration (sec.)	Change in heart rate/min.
Noradrenaline 2 µg. (10 cases)	Before ..	27/15	40	-4
	After ..	35/19	105	-5
Noradrenaline 4 µg. (9 cases)	Before ..	35/20	40	-5
	After ..	48/25	120	-6

minute on tilting. The figures for average fall in blood pressure may have been unduly weighted by the results in Case 6, who had marked postural hypotension during the control study.

After treatment with methyldopa the average supine blood pressure of these patients was lower (183/87 mm. Hg) and the fall that occurred on tilting was slightly greater than before treatment (average tilted blood pressure 148/80 mm. Hg). The average cardiac output after treatment fell from 5.3 litres a minute in the supine position to 4.0 litres a minute on tilting, a difference of -1.3 litres a minute. This fall in cardiac output, although slightly larger than that before methyldopa treatment, was not significant statistically.

*Response to Valsalva Manœuvre.* In 8 of the 10 patients the overshoot in arterial pressure following the Valsalva manœuvre was completely abolished after treatment with methyldopa (Fig. 1). In the remaining 2, there was evidence of some blocking of the overshoot, but this was only partial.

*Effect of Pressor Amines.* A slight increase in the pressor effect of a given single intravenous dose of noradrenaline was noted after treatment with methyldopa (Table III). More striking however was the obvious prolongation of this effect which was seen even in cases where the magnitude of the pressor response remained unaltered (Fig. 2). With the doses of noradrenaline employed, the blood pressure in control studies returned to the resting level in less than 60 seconds in all cases, whereas after methyldopa the duration of pressor action was increased by a factor of 2 to 5 times. Some reflex bradycardia developed after noradrenaline in the majority of cases, and this response was unchanged after methyldopa.

The pressor effect of tyramine was increased after methyldopa in all 6 patients in whom it was

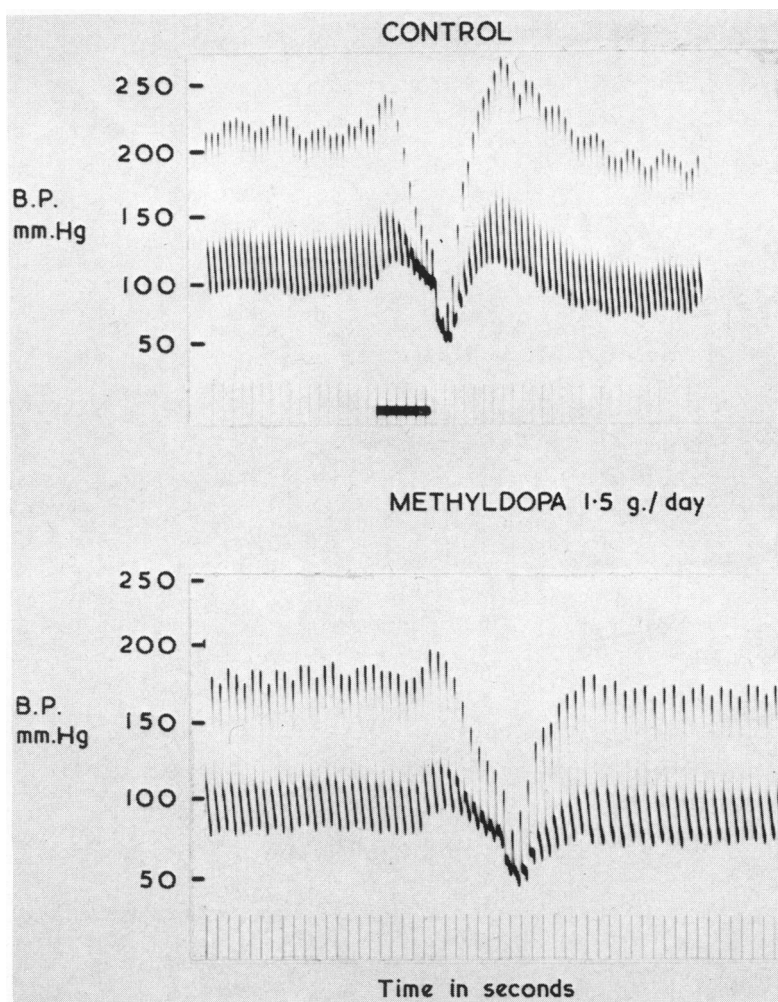


FIG. 1.—The response of the arterial pressure to performance of the Valsalva manoeuvre before and after treatment with methyldopa 1.5 g. daily for 10 days. The overshoot is blocked after treatment. Woman, aged 61.

studied (Fig. 3), the mean rise in blood pressure after a dose of 2.5 mg. being 18/10 mm. Hg before and 50/16 after treatment. This increased effect particularly concerned the systolic pressure. After an initial tachycardia, tyramine caused a quickening of the heart rate in some cases and a slowing in others; each individual tended to show the same response both before and after receiving methyldopa. There was some evidence that the duration of action of tyramine was prolonged after methyldopa from a control value of 3 to 5 minutes, but enough data were not available for a definite conclusion to be drawn.

#### DISCUSSION

The action of methyldopa shows differences from that of other known antihypertensive agents. In particular, it differs from the ganglion-blocking agents and the sympathetic-blocking drugs such as guanethidine in its ability to lower the supine blood pressure in many patients without causing

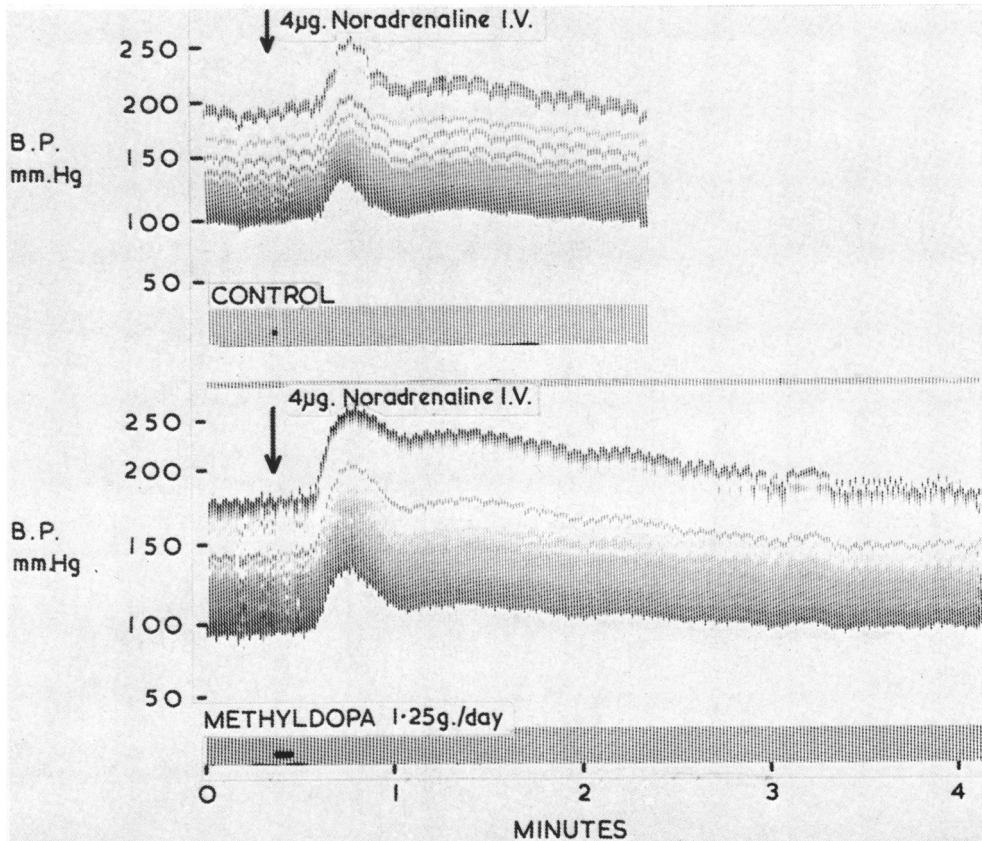


FIG. 2.—Pressor effect of 4  $\mu$ g. noradrenaline before and after treatment with methyldopa, 1.25 g. daily for 6 days. Woman, aged 51.

drastic postural hypotension, although some fall in blood pressure on standing usually occurs. Some part of its activity may be on central mechanisms, since drowsiness is a common and striking feature in the first days of treatment with the drug.

Apart from hydralazine, which has a stimulating effect on the heart, most other antihypertensive drugs reduce the supine cardiac output at the same time as they lower arterial pressure, unless heart failure is present. This has been shown in acute studies for the ganglion-blocking agents and guanethidine (Freis *et al.*, 1953; Dollery, Emslie-Smith, and Shillingford, 1961). Our observations suggest that methyldopa is no exception to this rule. The reduction in cardiac output with methyldopa was however slight and proportionately less than the fall in blood pressure in all but one case, indicating also a fall in the total peripheral resistance. Other workers have found no change in the supine cardiac output after 10 to 12 days' treatment with methyldopa (Bojs *et al.*, 1962; Pellegrini *et al.*, 1962).

The fact that methyldopa blocks the overshoot in arterial pressure following the Valsalva manoeuvre suggests a blocking action at some point along the sympathetic vasoconstrictor pathway. This sympathetic blockade might be expected to lead to an increased peripheral sensitivity to noradrenaline. In the present study the pressor effect of a single intravenous dose of noradrenaline was increased in magnitude after methyldopa in some patients, but this was inconstant and less striking

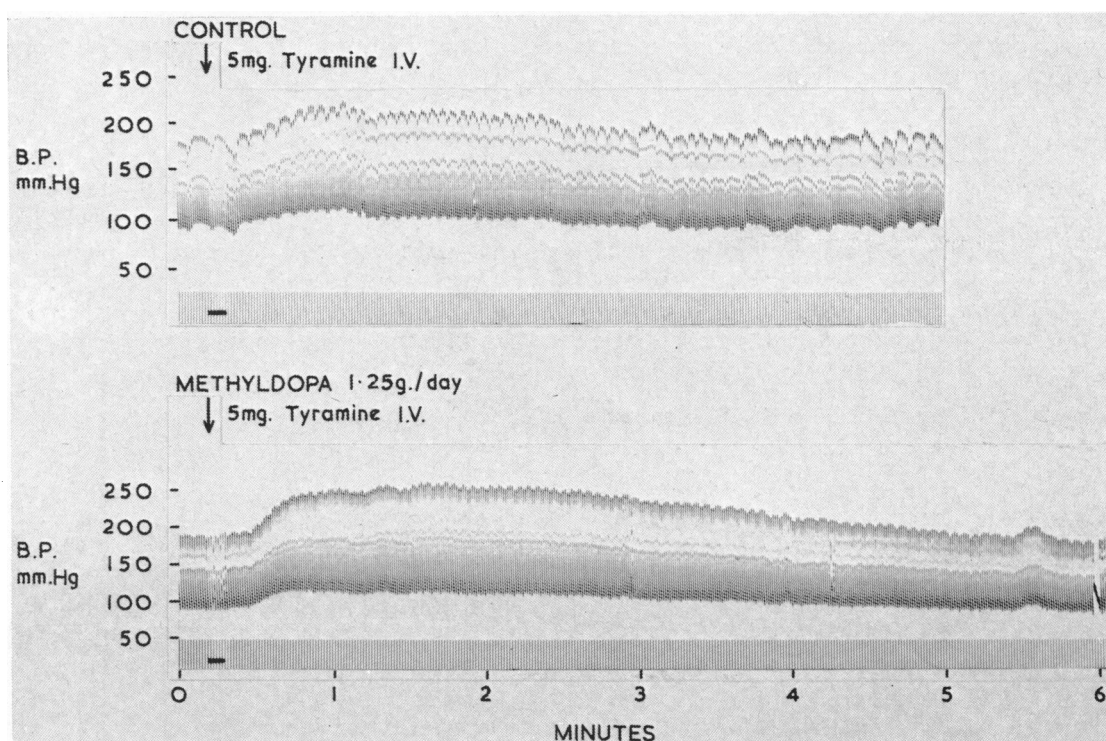


FIG. 3.—Pressor effect of 5 mg. tyramine before and after treatment with methyldopa 1.25 g. daily for 6 days (same patient as Fig. 2).

than the prolongation of action seen in every case. The increased duration of pressor action after a dose of noradrenaline could possibly be explained by an action of methyldopa in blocking the circulatory reflexes responsible for returning the pressure to baseline in an intact subject: this seems unlikely, however, since there was always at least as much reflex bradycardia in response to noradrenaline after methyldopa as before. In this connexion it is of interest that Hess *et al.* (1961) have found evidence in animal experiments that the ability of tissue to bind noradrenaline at the sites where it is stored is impaired after treatment with methyldopa.

Burn and Rand (1958) found the action of tyramine to be reduced in animals pretreated with large doses of reserpine, and postulated that the pressor effect of tyramine was mediated through liberation of stored noradrenaline. Reserpine-treated animals show noteworthy depletion of tissue noradrenaline, and a similar depletion has been found after methyldopa (Hess *et al.*, 1961). In this case, it might be expected that tyramine would have a reduced effect in patients treated with methyldopa. In fact our observations indicate that the reverse is the case, since patients receiving methyldopa in doses normally used clinically were uniformly more sensitive to the pressor action of tyramine. Stone *et al.* (1962) found that, in the dog, methyldopa was capable of antagonizing the pressor effect of phenethylamine and amphetamine, while that of noradrenaline was preserved, an observation that is consistent with the Burn-Rand theory.

However, there is other evidence that the pressor action of tyramine may be mediated directly or at any rate not by release of noradrenaline. Nasmyth (1960) estimated the total pressor amine content of the isolated perfused guinea-pig heart, and found no significant reduction in pressor amine content in hearts that had become insensitive to tyramine through repeated injection of the latter, as compared with controls. Under these conditions, however, the effect of injected noradre-

naline is reduced. Our results could perhaps best be explained by a direct action of tyramine on tissue receptors, the sensitivity of which is increased by an unknown mechanism after the administration of methyldopa.

#### SUMMARY

After four to ten days' treatment with methyldopa, the reduction in blood pressure in hypertensive patients was found to be accompanied by a bradycardia, by a slight fall in supine cardiac output, and also by a fall in calculated total peripheral resistance. On tilting feet downwards, some postural hypotension occurred, accompanied by a further reduction in cardiac output.

A small increase in sensitivity to the pressor effect of noradrenaline was seen in patients receiving methyldopa; the duration of action of a single dose of noradrenaline was greatly prolonged. The pressor action of tyramine was increased after methyldopa.

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